Date: 6/3/01

To: File P010012

From: Helen S. Barold, M.D.

RE: Preliminary Clinical Review of Guidant's Contak CD/Contak Renewal Heart Failure Devices and EasyTrak Lead System PMA

This is a preliminary review of the clinical section of the Guidant Contak CD Heart Failure Devices. It includes the clinical update that was received on June 2, 2001. This PMA was submitted in a modular form. All of the engineering and pre-clinical sections have been reviewed and accepted. The Statistical Review was performed by Gerry Gray, PhD.

Contact: Janet Cowan
US Principal Regulatory Affairs Associate
Guidant Cardiac Rhythm Management
4100 Hamline Avenue North
St. Paul, MN 55112-5798
Phone 651-582-3197
Fax 651-582-5134

Results provided for the following devices:

- Model 1822 Ventak CHF AICD
- Model 1823 Contak CD
- Models 4510/4511/4512/4513 EASYTRAK coronary venous single electrode pace/sense lead and accessories

Basic Device Description:

- Fully functional ICD and DDDR pacer
- Biventricular pacing capabilities, RV and LV leads are tied together.
- EasyTrak- 6F, LV-1 connector, tined, steroid eluting. The different models differ in length only. A guiding catheter is placed into the ostium of the CS, a guide wire is then placed into the CS vasculature and the lead is placed in an over the wire approach. A finishing wire is then placed into the lead to allow withdrawal of the guiding catheter without moving the lead.

Indications for use:

- Patients who have advanced symptomatic heart failure (NYHA III/IV) including left ventricular dysfunction (EF ? 0.35) and wide QRS complex (QRS >120 ms) while on heart failure drug therapy; and

- Patients who are at high risk of sudden cardiac death due to ventricular arrhythmias

These are patients that are already indicated for an ICD and would additionally be receiving biventricular pacing. The concept behind this type of therapy is that biventricular pacing allows for "resynchronization" of the ventricles in patients with intraventricular conduction delays, which may improve hemodynamics. By placing leads that stimulate both the right and the left ventricle, one can potentially program the timing of electrical stimulation that allows for an optimal cardiac output for an individual patient.
CRT= Cardiac Resynchronization Therapy; BiV= Biventricular

Study Objectives:

- * Primary - Slowing the progression of heart failure, as defined as all-cause death, heart failure-related hospitalization, and VT/VF events resulting in device therapy.
- Appropriate LV pacing thresholds, Biventricular (BiV) sensing, BiV lead impedance, lead safety and placement success rate.
- Improvement in functional status as measured by peak oxygen uptake, VE/VCO2 slope and a 6-min hall walk.
- Improvement in QOL
- Appropriate ATP conversion
- Safety as measured by incidence of EASYTRAK lead-related adverse events, appropriate VT detection times, incidence of severe device-related adverse events and peri-operative mortality.

Study Methods:

For the first 30 days after implantation, BiV pacing was not turned on. The ICD portion of the device was active in all patients all the time. The patients were then randomized to either BiV pacing ON or OFF. All patients receive devices, but in the No CRT group- the BiV pacing portion of the device is turned off, not the ICD portion, which remains on at all times.

The Initial study design was a randomized 3-month crossover study. 248 Patients were enrolled in what is now called the Phase I trial. The protocol was subsequently modified to a randomized 6-month parallel study, now called Phase II. After the 6-month point, all patients were allowed to have CRT turned ON.

Inclusion Criteria:	**Exclusion:**
– Standard ICD indications – Symptomatic heart failure despite optimal drug therapy (not specific NYHA Class) – LVEF <= 35% – QRS >= 120 ms – Age >18 – Normal sinus node function	– Meet general indication for permanent antibradycardia pacing – Chronic refractory atrial arrhythmias – Concomitant cardiac surgery – Unable to undergo device implant – Unable to comply w/follow-up – Have life expectancy of <6 months due to other medical conditions – Amyloid – HOCM – Requires in-hospital iv inotropes – Pre-existing leads that are not on the approved list – Women who are pregnant or not using birth control – Mechanical tricuspid valve – Involved in other cardiovascular clinical investigations

Implant Duration in Months:

Device	N	Mean	SD	Min	Max	Cumul.
Ventak CHF	57	23.4	12.7	0.2	39.7	1337
Contak CD and Easytrak	444	14.8	6.8	0.0	27.1	6577
Total	501	15.8	8.2	0.0	39.7	7913

They present and analyze **490** patients that were implanted and active at 31 days post-implant.

ENDPOINTS (for full description see page 19+ of Volume 2):

1) PRIMARY EFFICACY FOR CRT: Composite endpoint of: all-cause mortality, heart failure-related hospitalization, or VT/VF resulting in device therapy. These endpoints were taken from the PRECISE study, which is a randomized placebo controlled study of carvedilol. The endpoints are ranked by severity. The primary endpoint was powered to detect a 25% reduction in event rates.** It was assumed that the control event rates would be 15% death, 30% hospitalization for CHF and 20% VT/VF**

   Sample size was calculated to be 308 patients.

2) PRIMARY EFFICACY FOR LEADS: These are pacing thresholds, BiV sensing, BiV lead impedance

3) PRIMARY SAFETY FOR LEADS: adverse events specifically related to the leads. An acceptance boundary of 23% was used. This was based on historical data obtained in European studies.

4) There does not appear to be a primary safety endpoint for the system in general. It is listed as secondary endpoints.

RESULTS:

Baseline Characteristics:

Characteristic	**CRT = 248**	**No CRT = 253**
Age	66±10.5	66.3±10.5
Gender (%male)	84.3%	83.4%
NYHA Class %	II- 32.3% III- 59.7% IV- 8.1%	II- 32.8% III- 56.9% IV-10.3%
% RBBB	14.5	12.6
EF	21.3±6.6	21.6±6.6
% ACE -	85.55%	88.5%
% Beta-blocker	47.6%	45.8%
Etiology % ischemic	67.3%	70.4%
6 minute hall walk	315±6	315±6

Comments: Overall, the patients are on good medical regimens. There is a high percentage of males, the sponsor was able to adequately justify this by noting that not only are there more males with CHF, but also more that require an ICD. Approximately 1/3 are in class II HF, this amount changes to approximately ½ at the time of randomization. (Remember that the BiV pacing is not turned on until 1 month after implant.) Also 6-7% of patients are in class I HF at the time of randomization. Several things could accounts for this, including either a regression to the mean, a placebo effect of having a device in or simply better medical attention. This change in status should be kept in mind while interpreting the final data.

The sponsor has included an analysis of those patients with persistent advanced heart failure, defined as those that remain in class III/IV after the one-month waiting period. There are a total of 236 patients in this group (CRT=120; No CRT=116). These patients had roughly the same baseline characteristics as the entire group.

Primary endpoints: The composite of the three endpoints showed no statistical significance and individually, there was no difference in the death rate, hospitalization rate, adverse event rate for HF or recurrent VT/VF between the 2 groups.

Composite Endpoint Event	**CRT (N=245)**		**NCRT (N=245)**		Overall Reduction in Original Composite Endpoint	Overall Reduction in the Modified Composite Endpoint
	N	%	N	%		
Death from any cause	11	4.5	16	6.5	19% p=0.21	23% p=0.11
Hospitalizations	31	12	37	15.1		
AE for HF	15	6.1	28	11.4		
Recurrent VT/VF	33	13.5	37	15.1		

As noted above: It was assumed that the control event rates would be 15% death, 30% hospitalization for CHF and 20% VT/VF. The actual event rates were 6.5, 15.1 and 15.1% respectively. It is possible that given the lower than expected actual event rates, that the study is underpowered. The sponsor provides several reasons for the lower than expected event rates, including improvements in the current medical therapy for CHF and relatively short follow-up time. In addition to this, some of the decreases in hospitalizations and potentially even arrhythmias may be in part related to a placebo effect.

Primary Endpoint Subgroup Analysis for Advanced Heart Failure patients:

Composite Endpoint Event	**CRT (N=117)**		**NCRT (N=109)**		Overall Reduction in Original Composite Endpoint	Overall Reduction in the Modified Composite Endpoint
	N	%	N	%		
Death from any cause	11	9.4	10	9.2	25% p=0.19	29% p=0.11
Hospitalizations	22	18.8	26	23.9		
AE for HF	11	9.4	17	15.6		
Recurrent VT/VF	20	17.1	19	17.4		

The event rates for this group are much closer to the expected event rates, but it is not powered.

Deaths:

27 patients did during the therapy phase, but a total of 95 deaths were reported. There was no difference in the death rate between the 2 groups. After the therapy phase, 42 patients died of pump failure.

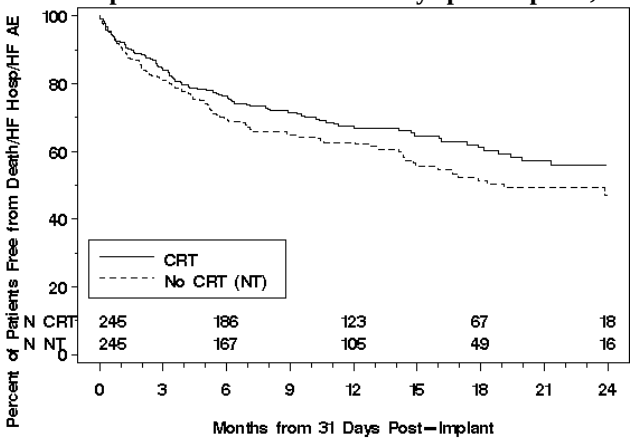
- CRT (11 deaths)
  - Cardiac, pump failure (4 deaths)
  - Cardiac, unknown (2 deaths)
- No CRT (16 deaths)
  - Cardiac, pump failure (9 deaths)
  - Unknown (3 deaths)

- Unknown (2 deaths)
- Non-cardiac (2 deaths)
- Cardiac, arrhythmic (1 death)
- Non-cardiac (3 death)
- Cardiac, ischemic (1 death)

Cause	CRT (N=245)	No CRT (N=245)	P-value
All cause	11 (4.5%)	16 (6.5%)	0.32
Cardiac, all categories	7 (2.9%)	10 (4.1%)	0.46
Cardiac, pump failure	4 (1.6%)	9 (3.7%)	0.16

Time to Death or First HF Hospitalization or First HF AE

All patients implanted and active at 31 days post-implant, N=490



*Log-Rank test p-value = .09

In the above figure, remember that all patients had therapy turned on at the 6-month point.

Secondary Therapy Endpoints:

1) Peak VO2- Interestingly, both groups showed an improvement at the 3 month point. The Control group had a minor decline at the 6-month point whereas the therapy group maintained the improvement, the difference between the 2 groups was not statistically significant (p=0.08).

   a) Advanced Heart Failure Patients: There is a clinically and statistically significant change at six months with treatment in this group. The delta is 2.1±0.8, p=0.11. There is almost no improvement in the control group. (n=160/236; CRT=85, NoCRT=75)

2) Change in VE/VCO2- Again both groups show an improvement, suggestive of a placebo effect, but at 6 months there was no significant improvement between the 2 groups.

   a) Advanced Heart Failure Patients: There is not a statistically significant improvement in the treatment group (p=0.16). But again, there is almost no improvement in the control group at 6 months. (n=160/236; CRT=85, NoCRT=75)

3) Change in 6-minute hall walk- Again, both groups showed significant improvement and in this case it carried over into the 3 and 6-month points. The treatment group trends toward a significant improvement over the control group (p=0.088).

   a) Advanced Heart Failure Patients: There is a statistically significant improvement in the treatment group over the control group, p=0.022. In this parameter, the control group does show some improvement across time. (n=188/236; CRT=98; NoCRT=90)

4) Change in Quality of Life- Again, both groups showed a significant improvement in their quality of life scores which speaks for a placebo effect. There was improvement at both the 3 and 6-month points. No difference between the groups.

All Patients	No CRT- Within Group Analysis		CRT- Within Group Analysis		Between Group Analysis- Incremental Change with CRT over No CRT	
Parameter	Est ±SE	p-val	Est±SE	p-val	Est±E	p-val
Baseline	41.9±1.1	<0.001	41.9±1.1	<0.001	0	
3 month	-4.9 ± 1.5	<0.001	-5.1±1.4	<0.01	-0.2±2.0	0.91
6 months	-5.1±2.0	0.01	-7.2±2.0	<0.01	-2.1±2.7	0.44

   a) Advanced Heart Failure Patients: There is a significant improvement in the treatment group as compared to control, p=0.023. (n=203/236; CRT=107, NoCRT=96)

Advanced Heart Failure	No CRT- Within Group Analysis		CRT- Within Group Analysis		Between Group Analysis- Incremental Change with CRT over No CRT	
Parameter	Est ±SE	p-val	Est±SE	p-val	Est±E	p-val
Baseline	52.3+1.6	<0.001	52.3+1.6	<0.001	0	
3 month	-5.5+2.3	0.019	-10.4-2.2	<0.001	-5.0+3.1	0.12
6 months	-5.6+3.3	0.095	-16.5+3.5	<0.001	-10.9+4.7	0.023

5) NYHA Functional Class- There was improvement in both groups, but no difference between groups, although the treatment group trended toward a better improvement (P=0.06). Over 50% of patients had no change in their functional group. Approximately 15% of patients had a worsening of functional class.

6 month Change in NYHA class	**CRT**		**No CRT**		P value
	N	%	N	%	
Decrease 2 or more	11	11.8	2	2.0	0.06
Decrease 1	21	22.6	27	27.6	
No change	49	52.7	53	54.1	
Increase 1	11	11.8	16	16.3	
Increase 2 or more	1	1.1	0	0.0	

a) Advanced Heart Failure Patients: More patients improved a NYHA class with treatment, p=0.03

6 month Change in NYHA class	**CRT =36**		**No CRT=38**		P value
	N	%	N	%	
Decrease 2 or more	11	30.6	2	5.3	0.03
Decrease 1	15	41.7	17	44.7	
No change	8	22.2	16	42.1	
Increase 1	2	5.6	3	7.9	

This table needs to be interpreted carefully as there are only 36 and 38 patients in each group. Also, a significant portion of the control group improved at least one class.

Conclusion of secondary endpoints: It is impressive that in a population which a disease that is notoriously progressive, there is a significant improvement in functional status both with and without therapy. I do not believe that this can be accounted for by "improvements in CHF therapy" alone, rather I believe it speaks at least partially to a placebo effect. However, if the patients are analyzed by the heart failure class they are in at the time of randomization (one month after implant) and only those patients with advanced heart failure (class III/VI) are analyzed, the results are more encouraging. The table below shows the secondary functional endpoints at the 6-month point for those patients that have advanced heart failure at the time of implant and those that still had advanced heart failure at the time of randomization. Interestingly, there seems to be less of a placebo effect in those patients also.

Endpoint	**Comparison**	**Pre-implant**			**Randomization**		
		N	**6 Mo Change**	**P-val**	**N**	**6 Mo Change**	**P-val**
Peak VO2 (ml/kg/min)	Within CRT	241	0.9 +/- 0.4	0.030	159	2.2 +/- 0.6	<0.001
	Within No CRT		-0.5 +/- 0.4	0.26		0.1 +/- 0.5	0.83

Endpoint	Comparison	Pre-implant			Randomization		
		N	6 Mo Change	P-val	N	6 Mo Change	P-val
	Between Groups		**1.3 +/- 0.5**	**0.017**		**2.1 +/- 0.8**	**0.012**
VE/VCO2 Slope	Within CRT	241	-2.0 +/- 1.1	0.084	159	-4.2 +/- 2.0	0.042
	Within No CRT		-0.4 +/- 1.2	0.73		-0.4 +/- 1.6	0.82
	Between Groups		**-1.6 +/- 1.6**	**0.32**		**-3.8 +/- 2.5**	**0.13**
6 Min Walk (m)	Within CRT	287	46 +/- 13	<0.001	187	78 +/- 16	<0.001
	Within No CRT		10 +/- 14	0.48		30 +/- 14	0.041
	Between Groups		**37 +/- 19**	**0.049**		**48 +/- 21**	**0.022**
QOL (score)	Within CRT	302	-10.5 +/- 2.5	<0.001	199	-16.2 +/- 3.5	<0.001
	Within No CRT		-4.4 +/- 2.6	0.096		-5.8 +/- 3.3	0.081
	Between Groups		**-6.0 +/- 3.5**	**0.089**		**-10.4 +/- 4.7**	**0.029**

Those patients with advanced heart failure at the time of randomization who are treated with CRT have significant improvements in their peak VO2, 6 minute hall walk and QOL score. So those patients with persistent advanced heart failure appear to improve with the CRT therapy. It is possible that at the time of implant, a percentage of these patients have a component of decompensated heart failure that will improve with medical therapy alone. CRT in those patients will unlikely have additional benefit.

Based on Holter data, 99.6% of the CRT patients had 100% ventricular pacing during the study. Of the remaining patients, 0.4% had transient inappropriate pacing or sensing that was corrected by reprogramming the device. So it appears that close to all the patients in the treatment group were receiving biventricular pacing.

Safety: This is an overall safety analysis. The safety profile for the advanced heart failure patients will be presented at the time of the panel meeting.

1) ATP conversion Efficacy: Success rate was 63.6%, which is much lower than the predicted value of 85%. The sponsor justifies this by stating that operative ATP practices have changed over time. The spontaneous ATP conversion rate was 88%, which is adequate to justify this endpoint. More importantly, the added BiV pacing does not interfere with the primary function of the cardioverter defibrillator.
2) Ventricular Tachycardia Detection Time: no increase in detection time with tying the RV and LV lead together

3) Severe, Device-Related Adverse Events and Operative Mortality- The hypothesized rate was 20%. The actual rate was 1.2%. The operative mortality was 3.4% for thoracotamy and 2.0% for transthoracic procedures. There was however 12/567 (2.1%) peri-operative mortality.

4) Hospitalization for Heart Failure:

Reasons for Hospitalization	**CRT**	**No CRT**	**Total**
CHF	48	48	96
Cardiac-other	39	29	68
Noncardiac	28	23	51
Total	115	100	215

Each hospitalization is counted in the above table.

EasyTrak Lead Endpoints: These are for all patients. The analysis for the advanced heart failure patients will be presented at the time of the panel meeting.

1) Pacing thresholds: Pacing thresholds are stable after the one month point, which is consistent with steroid eluting leads at about 1.9V $\pm$1.3V

2) Sensing- sensing was good at >9 mV.

3) Impedance- again, good and consistent

The performance of threshold, sensing and impedance for the BiV pacing using EasyTrak LV leads is fine and meets the proposed endpoints.

4) Safety- 72 or 13.9% of patients had a lead related adverse event. LV lead dislodgment was the most common at 29 or 6.5%. Serious complications included 5 cases of CS perforation and 1 guide wire fracture which was removed by a snare.

   - Unsuccessful implants- Of the 69 patients that the EasyTrak lead could not be placed in: 29 (42%) were due to problems locating or cannulating the CS. There were 5 (7.2%) instances of CS dissection or perforation.

The table below contains the incidence of coronary sinus trauma with the EasyTrak lead and delivery system. In the Companion study, there were a greater number of CS traumas identified. The DSMB for that study recommended some implantation guidelines that may decrease this incidence. It appears that the lead itself is not responsible for the traumas, rather the delivery system and its use.

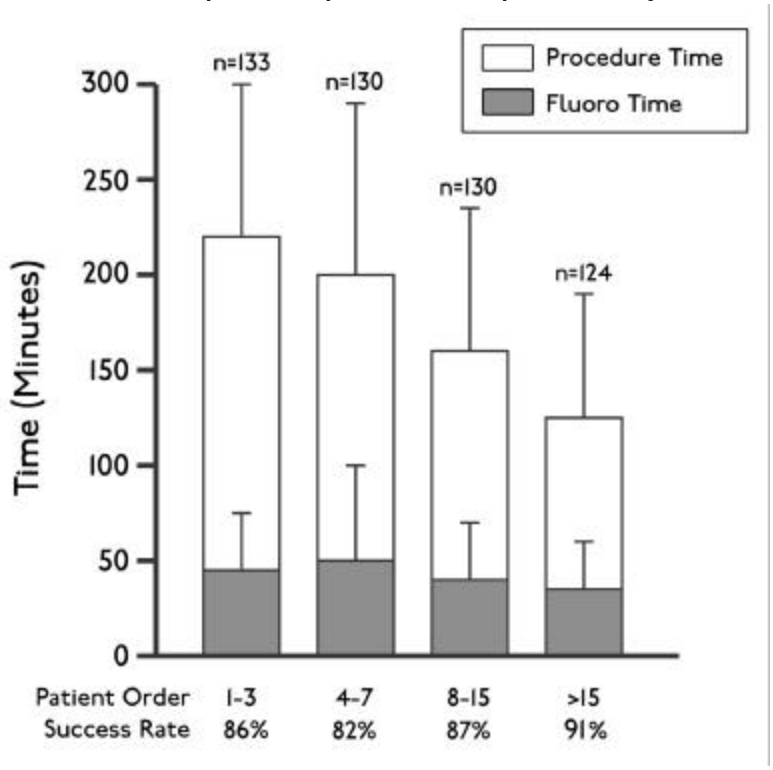
Coronary Sinus Trauma	**INCIDENCE**			**TOTALS**	**OUTCOMES**				
	Contak CAP	**Contak CD**	**COMPANION**		**Resolved without Intervention**	**Intervention Required**	**Death**		
	N=237	**N=517**	**N=620**	**N=1374**			**N=1374**		
							Related	Unrelated	Unknown
Dissection	4(1.7%)	5(1.0%)	11(1.8%)	20(1.5%)	20(100%)	0(0.0%)		2*	1
Perforation	3(1.3%	5(1.0%)	9(1.5%)	17(1.2%)	16(94%)	1 (6%)	1*	1, 1*	1*

Tamponade	0(0.0%	0(0.0%)	2(0.3%)	2(0.1%	0(0.0%)	2(100%)	1*		
Totals	7(3.0%)	10(1.9%)	22(3.5%)	39(2.8%)	36(92.3%)	3(7.7%)	2(0.1%)	4(0.3%)	2(0.1%)

* Based on Investigational center information. Events Committee adjudication pending.

Procedure Time: The time appears to decrease with investigator experience.

All patients implanted or attempted with EasyTrak lead, N=517



Conclusions on safety: The leads themselves appear to be working well, but there is an issue with implantation. This related to some of the issues seen in the Companion study. New implantation guidelines may help this situation. The system as a whole appears to be safe in that they have met their safety endpoints. I am concerned with some of the generator failures. There are at least 5 reported failures, 4 of which required new implants. This seems to be a high rate. A safety profile for the advanced heart failure patients will need to be performed.

Summary: The sponsor did not meet any of the primary effectiveness endpoints even when the subgroup analysis was performed. In the advanced heart failure patients, it does appear that the device is effective with regards to the secondary endpoints of peak VO2, 6-minute hall walk, QOL and change in NYHA class. We will have to clarify with the statistician if they are adequately powered. Also note the sponsor underestimated the event rates that their primary endpoints are based on. This suggests the study may underpowered to meet those endpoints. The event rates in the subgroup appear closer to the estimated values, but there are not enough patients for it to be considered adequately powered. The sponsor has shown that the addition of biventricular pacing to an ICD does not interfere with the primary function of the ICD.